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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/608,713	06/30/2000	Hideo Ago	SHIM-007	2056

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EXAMINER	
LY, CHEYNE D	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/608,713	AGO ET AL.	
	Examiner	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *October 22, 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-39* is/are pending in the application.

4a) Of the above claim(s) *19-29,32 and 34-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,31,33 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *19-39* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 22, 2003 has been entered.

2. Claims 19-29, 32, and 34-36 have been withdrawn.

3. Claims 30, 31, 33, and 37-39 are examined on the merits.

PRIORITY

4. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). However, foreign applications JAPAN 11-188630, filed July 02, 1999, and JAPAN 11-192488, filed July 07, 1999 do not disclose the three-dimensional structural coordinate of an NS5B HCV polymerase. It is noted the foreign applications are directed to a generic HCV polymerase while the instant claimed invention is directed to NS5B HCV polymerase. Therefore, the instant application does not receive the priority benefit of foreign applications JAPAN 11-188630, filed July 02, 1999, and JAPAN 11-192488, filed July 07, 1999.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 30, 31, 37, and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Specific to claim 30, lines 14-15, lines 14-15 cause the claim to be vague and indefinite due the use of the limitation of "complementary" of test compound to an active site to determine a HCV polymerase inhibitor. The said limitation of "complementary" does not make clear the criteria being used to determine that a test compound inhibits a HCV polymerase. Is a compound an inhibitor because it is complementary to a HCV polymerase or does the said compound have to change the activity of the HCV polymerase through some interaction other than inhibition? Clarification of the metes and bounds is required. Claims 31, 37, and 38 are rejected due to being dependent from claim 30.

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 30, 31, 33, and 37-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a crystal structure of HCV polymerase using $NS5B_{570, 544, 536 \text{ and } 531}$, does not reasonably provide enablement for all HCV polymerases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

10. This rejection is maintained with respect to claims 30, 31, 33, and 37-39 as recited in the previous Office Action, mailed March 22, 2003.

RESPONSE TO APPLICANT'S ARGUMENT

11. Applicants argue that Drenth and New Focus fail to provide any evidence indicating that experimental parameters disclosed in the specification do not result in predictable crystallization

of HCV polymerase NS5B crystal structures. Further, the said two references do not provide adequate support that the instant specification does not enable one of skill in the art to practice the full scope of claims without undue experimentation. Applicants' argument and pointed to support have been fully considered and found to be unpersuasive as discussed below.

12. Applicants' argument that nothing in Drenth or New Focus contradicts Applicants' assertions that predictable HCV polymerase NS5B crystallization conditions disclosed in the specification or that undue experimentation is not required to practice full scope of the claims has been fully considered and found to be unpersuasive. It is noted that neither Drenth or New Focus contradicts Applicants' assertions that the instant specification is enabled for one of skill in the art to crystallize HCV polymerase NS5B crystallization as directed to HCV polymerase using $NS5B_{570, 544, 536 \text{ and } 531}$ (Examples 1-3, Pages 20-27). The citation of Drenth and New Focus is only to support that currently the art of crystallography is unpredictable. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Therefore, for any invention, which is not enabled for any person skilled in the art to use said invention commensurate in scope with these claims, one of skill in the art would require undue experimentation to practice the claimed invention.

13. Specific to Drenth, Applicants acknowledge, "Drenth indicates that the proper experimental conditions that lead to predictable crystallization can be determined in some circumstances. Applicants note that Drenth states the results are "usually" unpredictable, meaning that they are not always unpredictable. Applicants' arguments via citation of Drenth above strengthen the Office's assertion that the art of crystallography is unpredictable. As

directed Applicant's pointed to citation of proper experimental conditions that lead to predictable crystallization can be determined in some circumstances, Applicants are submitting that crystallization is predictable in some circumstances. Therefore, one of skill in the art would be required to perform undue experimentation to determine under which circumstances would lead to a predictable crystallization effort. The same rationale is applied to Applicants argument that "results are 'usually' unpredictable, meaning that they are not always unpredictable", therefore, it is mostly by chance that one of skill in the art would be able to practice the claimed invention commensurate in scope with these claims with success.

14. Specific to the Adachi et al. reference, Applicants argue that the different crystal qualities are merely referring to sequence-dependent differences in structural characteristics of the various NS5B constructs test, and are not referring to inconsistent or unpredictable methods of preparing crystals. Applicants' argument has been fully considered and found to be unpersuasive due to said argument does not help Applicants overcome the lack of enablement in scope of the instant claimed invention as discussed above and re-iterated below.

15. It is re-iterated that applicants have disclosed information to enable one skilled in the art to make a usable crystal of the HCV polymerase using NS5B570, 544, 536 and 531 (Examples 1-3, Pages 20-27). However, the breadth of claims 30, 31, 33, and 37-39 includes HCV polymerase NS5B570, 544, 536 and 531 crystals and modified versions of HCV polymerase crystals, which go beyond the crystals cited in Examples 1-3 (NS5B570, 544, 536 and 531).

16. Applicants provide a publication by Adachi et al. to support the predictability of the art of crystallizing HCV polymerase. Applicants argue that the disclosure and cited support enable the full scope of the claims 30, 31 and 33 regard to the limitations of the method for identifying a

HCV polymerase inhibitor. Applicants' arguments, pointed to enablement support for NS5B570, 544, 536 and 531, and cited publications have been fully considered and they have been found to be unpersuasive.

17. It is well documented that protein crystallization is in essence a trial-and-error method, and the results are usually unpredictable (Drenth, J.). Further, as recently as November 1, 2002, Science published a New Focus article depicting the current state of the art for protein crystallization that supports the unpredictability of the art. Protein crystallization is still a trial and error process because the current technology for producing protein for the crystallization process is unpredictable, which results in high failure rate for proteins that are being crystallized. Therefore, researchers continue to have trouble generating sufficient protein required for the crystallization process (Science, 2002). The citation of a few successful but isolated crystal structures of HCV polymerase does not help the instant applicant to overcome the overwhelming evidence provided by New Focus stating the unpredictability of the art of protein crystallization. For example, "[s]o far, these projects have targeted more than 18,000 proteins but solved the structures of only about 200" (Page 948, Column 3, lines 4-6).

18. Therefore, it is further re-iterated that it is unreasonable to expect one skilled in the art to use the information disclosed for one specific crystal to make other of predictable quality that are different from the crystal disclosed in the specification without undue experimentation.

CLAIM REJECTIONS - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 30, 31, 33, and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (US 6,183,121 B1) in view of In re Gulack, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983) taken with Bressanelli et al. (1999).

22. This rejection is maintained with respect to claims 30, 31, 33, and 37-39 as recited in the previous Office Action, mailed March 22, 2003.

RESPONSE TO APPLICANTS' ARGUMENT

23. Applicants argue that the Bressanelli et al. (November 09, 1999) prior art document is published after the claimed priority date of the instant application (Japan 11-188630, July 02, 1999 and Japan 11-192488, July 07, 1999) where in the translation of said foreign priority has been provided. Applicants' arguments have been fully considered and found to be unpersuasive due the foreign priority documents do not disclose the claimed subject matter. (See Priority §)

24. It is re-iterated that Kim et al. discloses a method that uses "atomic coordinates of all the amino acids of NS3 helicase according to FIG. 1 .+-. a root mean square deviation from the

backbone atoms of said amino acids of not more than 1.5 .ANG., to generate a three-dimensional structure of molecule comprising a NS3 helicase-like binding pocket, as in instant claim 30. For the first time, the present invention permits the use of molecular design techniques to identify, select and design chemical entities, including inhibitory compounds, capable of binding to NS3 helicase-like binding pockets—in particular, the oligonucleotide binding pocket of NS3 helicase" (Column 14, lines 27-38), as instant claims 31 and 33. "Thus, any compound which fits into a pocket comprising the structural coordinates .+-. a root mean square of 1.5 .ANG. or less from the backbone atoms of these amino acids is a potential inhibitor of the NS3 helicase" and data disclosed in Table 1 suggest the inhibitory nature of potential inhibitors (Column 31, 36-45 and Table 1), as in claims 37-39.

25. Even though the method disclosed by Kim et al. does not specify that the three-dimensional structural coordinate is derived from a HCV polymerase, the specific limitations of three-dimensional structural coordinate is derived from a HCV polymerase in this instant case do not distinguish the invention from the prior art in term of patentability because they are descriptive nonfunctional subject matter. Further, the Examiner has interpreted the instant claimed invention as a computer implemented method (pages 24-25).

26. In re Gulack defines nonfunctional descriptive material, as when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in term of patentability. Also, the MPEP indicates that descriptive material that cannot exhibit any functional interrelationship with the way in which computing processes are performed does not constitute a statutory process, machine, manufacture or composition (MPEP § 2106 (IV)(B)(b)). Specific to the instant case, the three-dimensional structural

coordinates derived from a HCV polymerase of a method for identifying a HCV polymerase inhibitor are merely stored so as to be read or outputted by a computer without creating any functional interrelationship, either as part of the stored data or as part of the active steps of the method for identifying a HCV polymerase inhibitor, then such descriptive material alone does not impart functionality either to the data as so structured, or to the computer.

27. Bressanelli et al. discloses a crystal structure of the RNA-dependent RNA polymerase of hepatitis C virus where the catalytic domain of the HCV RdRp consists of the 531 amino-terminal residues of NS5B. As a key step to developing specific anti-HCV drugs that interfere with viral replication (Page 13034, lines 23-26).

28. Clearly, an artisan of ordinary skill in the art at the time of the instant invention would have been motivated to partake the concept emphasized by Kim et al. for a method that uses of molecular design techniques to identify, select and design chemical entities, including inhibitory compounds based on the 3-dimensional structure of a polymerase and apply such method to the crystal structure for RNA-dependent RNA polymerase of hepatitis C virus as disclosed by Bressanelli et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the method taught by Kim et al. with the crystal structure coordinates of the RNA-dependent RNA polymerase of hepatitis C virus disclosed by Bressanelli et al. for identifying a HCV polymerase inhibitor.

CLAIM REJECTIONS - 35 USC § 103

29. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

30. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

31. Claims 30, 31, 33, and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (US 6,183,121 B1) in view of In re Gulack, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983).

32. Kim et al. discloses a method that uses "atomic coordinates of all the amino acids of NS3 helicase according to FIG. 1 .+-. a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 .ANG., to generate a three-dimensional structure of molecule comprising a NS3 helicase-like binding pocket. The polypeptide, NS3 helicase, of Kim et al. is a derivative of NS5B HCV polymerase (column 1, lines 47-67), as in instant claim 30.

33. For the first time, the present invention permits the use of molecular design techniques to identify, select and design chemical entities, including inhibitory compounds, capable of binding to NS3 helicase-like binding pockets—in particular, the oligonucleotide binding pocket of NS3 helicase" (Column 14, lines 27-38), as instant claims 31 and 33.

34. "Thus, any compound which fits into a pocket comprising the structural coordinates .+-. a root mean square of 1.5 .ANG. or less from the backbone atoms of these amino acids is a potential inhibitor of the NS3 helicase" and data disclosed in Table 1 suggest the inhibitory nature of potential inhibitors (Column 31, 36-45 and Table 1), as in claims 37-39.

35. Even though the method disclosed by Kim et al. does not specify that the three-dimensional structural coordinate as specified by the instant claims, the specific limitations of three-dimensional structural coordinate is derived from a NS5B HCV polymerase in this instant case do not distinguish the invention from the prior art in term of patentability because they are descriptive nonfunctional subject matter. Further, the Examiner has interpreted the instant claimed invention as a computer implemented method (pages 24-25).

36. In re Gulack defines nonfunctional descriptive material, as when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in term of patentability. Also, the MPEP indicates that descriptive material that cannot exhibit any functional interrelationship with the way in which computing processes are performed does not constitute a statutory process, machine, manufacture or composition (MPEP § 2106 (IV)(B)(b)). Specific to the instant case, the three-dimensional structural coordinates derived from a HCV polymerase of a method for identifying a HCV polymerase inhibitor are merely stored so as to be read or outputted by a computer without creating any functional interrelationship, either as part of the stored data or as part of the active steps of the method for identifying a HCV polymerase inhibitor, then such descriptive material alone does not impart functionality either to the data as so structured, or to the computer.

37. Clearly, an artisan of ordinary skill in the art at the time of the instant invention would have been motivated to partake the concept emphasized by Kim et al. for a method that uses of molecular design techniques to identify, select and design chemical entities, including inhibitory compounds based on the 3-dimensional structure of a polymerase such a derivative of a NS5B HCV polymerase. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the method taught by Kim et al. with the crystal structure coordinates of the NS5B HCV derivative for identifying a HCV polymerase inhibitor.

CONCLUSION

38. NO CLAIM IS ALLOWED.

39. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 193), and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 872-9306.

40. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (703) 308-3880. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

41. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

42. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

C. Dune Ly
12/18/03

ARDIN H. MARSCHEL
PRIMARY EXAMINER